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Synthesis and Structural Investigation of Biologically Active Complexes of 4-Acetyl-2-(acetylamino)-5-dimethyl-Δ^2-1,3,4-thiadiazole with Zn(II), Hg(II), Cd(II) and Cu(II)

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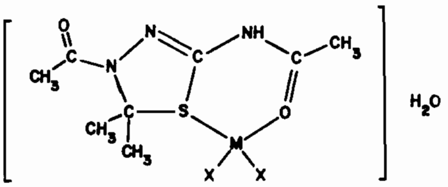
Abstract

4-Acetyl-2-(acetylamino)-5-dimethyl-Δ^2-1,3,4-thiadiazole (AAT) has been used to obtain the complexes of the general formula $[M-(AAT)X_2]\cdot H_2O$ where M(II) = Zn, Hg, Cd and Cu, and X = Cl or ½ SO_4. The complexes have been characterized on the basis of their elemental analysis, molar conductance, magnetic susceptibility and spectral data. Probable structures for the complexes have been proposed on the basis of their physico-chemical properties. The fungitoxicity of AAT and the isolated complexes has been tested on pathogenic fungi.

Introduction

Thiadiazole derivatives have been reported to be biologically versatile compounds, possessing antiviral [1], antibacterial [2], antipyretic [3], fungicidal [4], and analgesic [5] activities. The importance of the toxicity of the $-N-\overset{|}{\underset{|}{C}}-S-$ moiety has been well established in many fungicides and the presence of the thiadiazole ring is probably responsible for their fungicidal activity [6–7]. It is known that the metal complexes have greater activity than the coordinating agents themselves [8]. Furthermore, it is becoming increasingly clear that zinc plays a vital role in biological processes. Zinc deficiency can cause unusual disorders in the development of the body, disorders in the metabolic system and the prostate gland and can result in mental retardation. Hence it seemed worthwhile to study the complexation of AAT with divalent zinc and other bivalent metals. In the present communication, the authors report the isolation and characterization of Zn, Hg, Cd and Cu complexes with AAT and the fungicidal activities of the ligand and complexes on pathogenic fungi. The proposed structure of the complexes is as follows:



M = Zn(II), Hg(II), Cu(II), Cd(II) and X = Cl or ½ SO_4

Experimental

All chemicals used in this work were reagent grade and used without further purification. AAT was prepared and purified by the recommended method [9]. The complexes were prepared by the following method.

50 ml of a 0.05 M ethanolic solution of a metal salt was mixed with 50 ml of 0.05 M solution of AAT in acetone and the mixture was stirred for about 10 min. The precipitate which formed was filtered off, washed with ethanol, and dried under reduced pressure.

Physical Measurements

The Zn, Hg, Cd and Cu contents of the complexes were estimated by standard methods. Carbon, hydrogen, nitrogen, and oxygen were determined using a Buehler Apparatus for Microstructural Analysis, Federal Republic of Germany. The analytical results are given in Table I.

The magnetic susceptibility of the complexes was determined by Gouy's method at room temperature (27 °C) and the calculations were made using computed values of pascal constants for diamagnetic corrections.

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TABLE I. Analytical Data, Melting Point, Color, Magnetic Moment and Conductance Data of the Complexes.

Complex	Color	M.P. (°C) (Found)	C% Calcd. (Found)	H% Calcd. (Found)	N% Calcd. (Found)	S% Calcd. (Found)	O% Calcd. (Found)	M%[a] Calcd. (Found)	Cl% Calcd. (Found)	Ω	μ_{eff} (BM) (27 °C)
[Zn(AAT)Cl$_2$]·H$_2$O	White	195	25.99 (26.10)	4.06 (4.00)	11.37 (11.50)	8.66 (8.60)	12.99 (13.20)	17.70 (17.90)	19.22 (19.20)	10.00	Diamagnetic
[Hg(AAT)Cl$_2$]·H$_2$O	White	185	19.03 (19.00)	2.97 (2.98)	8.32 (8.40)	6.34 (6.30)	9.51 (9.52)	39.75 (39.80)	14.07 (14.00)	12.00	Diamagnetic
[Cd(AAT)Cl$_2$]·H$_2$O	White	>200	23.05 (23.00)	3.60 (3.62)	10.08 (10.12)	7.68 (7.72)	11.53 (11.60)	26.99 (27.10)	17.05 (17.10)	11.00	Diamagnetic
[Cu(AAT)SO$_4$]·H$_2$O	Yellowish green	185	24.46 (24.40)	3.82 (3.84)	10.69 (10.70)	16.30 (16.50)	28.53 (28.60)	16.19 (16.30)	– –	10.50	1.74

[a] M = the metal in the complex.

Conductance measurements were made on 10^{-3} M solutions of the complexes in nitromethane using a Toshniwal conductivity bridge.

The electronic spectra of the chelating agent and the complexes were recorded on a Varian Cary, model 219, automatic recording spectrophotometer.

The infrared spectra of the ligand and the complexes were recorded on a Perkin-Elmer model 983 G spectrophotomer in CsI pellets in the range 4000–200 cm^{-1}.

The antifungal activity of the ligand and the complexes was assayed against three pathogenic fungi, *Alternaria* (Sp.), *Paecilomyces* (Sp.) and *Pestalotia* (Sp.). Dimethyl sulfoxide was used as a solvent for preparing different concentrations (0.01% and 0.1%) of the chelating agent and metal complexes. The growth inhibition percentage was calculated on the basis of the average diameter of the fungal colony.

$$\text{Percentage Inhibition} = \frac{(C - T) \times 100}{C}$$

where C = diameter of the fungus colony in the control plates after 96 h, and T = diameter of the fungus colony in the treated plates after 96 h. The values of percentage inhibition of the complexes and the ligand are given in Table II.

Results and Discussion

The elemental analyses of the complexes showed that Zn, Hg, Cd and Cu combine with AAT to form complexes of composition [M–(AAT)X$_2$]·H$_2$O. All the complexes are insoluble in benzene and carbon tetrachloride but fairly soluble in acetone, methanol, nitromethane, DMF, DMSO, and acetonitrile. The solubility behavior suggests a monomeric structure for these complexes. The low values of molar conductance in nitromethane indicate that the complexes are non-ionic. Zn(II), Cd(II) and Hg(II) being d^{10} ions do not show d–d transitions and hence the stereochemistry of their complexes cannot be determined from ultraviolet and visible spectra. The structures of these complexes have been derived on the basis of infrared spectra and magnetic moment measurements.

Magnetic Moments

The magnetic moment values obtained for Zn(II), Hg(II) and Cd(II) complexes showed them to be diamagnetic and presumably with a tetrahedral geometry. The value μ_{eff} = 1.74 BM for [Cu(AAT)-SO$_4$]·H$_2$O showed that it was paramagnetic and possibly square planar.

Electronic Spectra

No conclusion concerning the stereochemistry of the Cu(II) complex under study can be drawn from

TABLE II. Fungicidal Screening Data of Complexes and the Free Ligand.

Compound	Average Percentage Inhibition after 96 h					
	Organism *Alternaria* (Sp.) Conen used		Organism *Paecilomyces* (Sp.) Conen Used		Organism *Pestalotia* (Sp.) Conen Used	
	0.01%	0.1%	0.01%	0.1%	0.01%	0.1%
$[Zn(AAT)Cl_2]\cdot H_2O$	40.0	58.0	40.0	60.4	49.0	65.0
$[Cd(AAT)Cl_2]\cdot H_2O$	50.0	64.0	50.0	79.0	52.0	78.0
$[Hg(AAT)Cl_2]\cdot H_2O$	55.0	75.0	60.0	80.0	64.0	86.0
$[Cu(AAT)SO_4]\cdot H_2O$	60.0	89.0	70.0	95.0	85.0	98.0
AAT	35.0	40.0	36.0	41.0	40.0	45.0

the magnetic data alone. The electronic spectrum of $[Cu(AAT)SO_4]\cdot H_2O$ complex showed a broad band at 15400 cm^{-1} corresponding to a combination of $^2B_{1g} \rightarrow {}^2A_{1g}$, $^2B_{1g} \rightarrow {}^2B_{2g}$ and $^2B_{1g} \rightarrow {}^2E_{1g}$ transitions in the D_{4h} symmetry, most probably with a square planar configuration [10, 11]. In the case of the zinc and cadmium complexes the intense bands at 28,000 and 30,800 cm^{-1}, respectively, are probably due to charge transfer transitions.

Infrared Spectra

An assignment of the important infrared absorption bands is based on the study of the infrared spectra of the free ligand and its metal complexes. An absorption band appearing at 3400 cm^{-1} can be assigned to a ν(N–H) vibration. The bands at 1635 cm^{-1} and 910 cm^{-1}, respectively, can be attributed to ν(C=N) and ν(N–N) bands. The peak occurring at 656 cm^{-1} is due to symmetric ν(C–S) vibration. The ν(C=N) and ν(N–N) bands present at 1635 and 910 cm^{-1}, respectively, in the ligand remain at the same positions in the spectra of the complexes suggesting that none of the nitrogen atoms of the thiadiazole ring is taking part in bonding with the metal. The ν(C–S) vibration is shifted from 656 cm^{-1} to 626 cm^{-1} on complex formation indicating the coordination through the S atom of the thiadiazole ring. The ν(C=O) vibration of the $-NH-CO-CH_3$ group in free AAT located at 1680 cm^{-1} is shifted downwards by about 30 cm^{-1} in the spectra of the complexes suggesting the coordination of the oxygen of the carbonyl group to the metal ion. In addition to the above changes, new bands which appeared in the spectra of the complexes in the regions 550–540 cm^{-1} and 390–330 cm^{-1} have been assigned to ν(M–O) and ν(M–S) bands, respectively. The three bands in the spectrum of the Cu(II) complex at 1230, 1125 and 1050 cm^{-1} are assignable to the bidentate SO_4^{2-} group. The absorption bands in the range 320–240 cm^{-1} are attributed to M–Cl stretching modes (M = Zn, Cd, Hg) which appear to have a tetrahedral environment around the metal ion [12–14]. Based on the above interpretations, it is concluded that AAT is bidentate in nature.

Evaluation of Antifungal Activity

The data on the antifungal activity exhibited by the ligand and its complexes are given in Table II. It is clear from the fungicidal screening data that the complexes are more fungitoxic than the free ligand. Further, it was noted that the toxicity of the metal complexes increases as the radius of the metal ion decreases from Zn to Hg.

A possible way of explaining the toxicity of the complexes has been proposed in the light of chelation theory [15]. It was suggested that the polarity of the metal ion would be reduced on complexation to considerable extent probably because of partial sharing of its positive charge with the donor groups and possible π-electron delocalization over the whole chelate ring, and as a consequence, the lipophilic character of the complex would increase which favors its permeation through the lipoid layers of fungus membranes. Furthermore, the mode of action of the compounds may involve the formation of a hydrogen bond through the –N=C– group with the active centers of the fungal cell constituents resulting in the interference with the normal cell process. It is well known that copper compounds are fungicidal and the literature survey revealed that fungi cause various destructive crop diseases *viz.*, potato blight, wilt *etc.* which necessitate large amounts of copper salts for the protection of plants [16]. Copper sulfate when used as a fungicide causes damage to the leaves [17]. Therefore, in order to minimize the quantity of metal ion salts it was thought worthwhile to synthesize coordination complexes to serve as fungicides.

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